FORM PTO-1390 U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE
TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: 9615 V/vmf

U.S. APPLN. NO. (If known, see 37 CFR 1.5) 10/009491

INTERNATIONAL APPLICATION NO.: PCT/EP00/05321	INTERNATIONAL FILING DATE: 08 JUNE 2000 (08.06.00)	PRIORITY DATE CLAIMED: 14 JUNE 1999 (14.06.99)

TITLE OF INVENTION: MESALAZINE CONTROLLED RELEASE ORAL PHARMACEUTICAL COMPOSITIONS

APPLICANT(S) FOR DO/EO/US: Roberto VILLA, Massimo PEDRANI, Mauro AJANI and Lorenzo FOSSATI

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [X] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [X] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] has been transmitted by the International Bureau. (see attached copy of PCT/IB/308)
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [ ] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [X] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] A translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Item 11. to 16. below concern document(s) or information included:

11. [X] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [X] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A **FIRST** preliminary amendment.
    [ ] A **SECOND** or **SUBSEQUENT** preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [X] Other items or information: INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT/IPEA/409), INTERNATIONAL SEARCH REPORT (PCT/ISA/210), APPLICATION DATA SHEET, ABSTRACT

U.S. APPLICATION NO. (if known, see 37 CFR 1.5) 10/009491	INTERNATIONAL APPLICATION NO. PCT/EP00/05321	ATTORNEY'S DOCKET NO. 9615 V/vmf

	CALCULATIONS PTO USE ONLY
17. [X] The following fees are submitted:	
BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)): Neither international preliminary examination fee (37 CFR1.482) nor international search fee (37 CFR1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO ..... $ 1,040.00	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO ..... $ 890.00	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO ..... $ 740.00	
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) ..... $ 710.00	
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) ..... $ 100.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 890.00
Surcharge of $130.00 for furnishing the oath or declaration later than months from the earliest claimed priority date (37 CFR 1.492(e)).	$

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	11 - 20 =	0	X $18.00	$
Independent claims	1 - 3 =	0	X $84.00	$
MULTIPLE DEPENDENT CLAIMS(S) (if applicable)			+ $280.00	$

TOTAL OF ABOVE CALCULATIONS =	$ 890.00
Reduction of ½ for filing by small entity, if applicable. Applicant claims Small Entity Status under 37 CFR 1.27. +	$ 445.00
SUBTOTAL =	$ 445.00
Processing fee of $130 for furnishing the English translation later than months from the earliest claimed priority date (37 CFR1.492(f)).	$
TOTAL NATIONAL FEE =	$ 445.00
Fee for recording the enclosed assignment (37 CFR1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +	$ 40.00
TOTAL FEES ENCLOSED =	$ 485.00
Amount to be refunded:	
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a. [X] A check in the amount of $ **485.00** to cover the above fees is enclosed.

b. [ ] Please charge my Deposit Account No. **25-0120** in the amount of $ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required by 37 CFR 1.16 and 1.17, or credit any overpayment to Deposit Account No. **25-0120**. A duplicate copy of this sheet is enclosed.

SEND ALL CORRESPONDENCE TO

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December 13, 2001

By Benoît Castel
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PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Roberto VILLA et al.

Box Non-fee Amendment

Serial No. (unknown)

GROUP

Filed herewith

Examiner

MESALAZINE CONTROLLED RELEASE ORAL PHARMACEUTICAL COMPOSITIONS

PRELIMINARY AMENDMENT

Commissioner for Patents

Washington, D.C. 20231

Sir:

Prior to the first Official Action and calculation of the filing fee, please amend the above-identified application as follows:

IN THE CLAIMS:

Please amend claims 3, 6 and 8-11 as follows:

--3.(Amended) Compositions as claimed in claim 1, wherein 5-aminosalicylic acid is inglobated in the molten lipophilic matrix by kneading, extrusion and/or granulation.

6.(Amended) Compositions as claimed in claim 1, comprising a gastro-resistant outer coating.

8.(Amended) Compositions as claimed in claim 1, in the form of tablets, capsules, minitablets, wherein the active ingredient is completely contained inside the lipophilic matrix.

9.(Amended) Compositions as claimed in claim 1, in the form of tablets, capsules, minitablets, wherein the active ingredient is dispersed both in the hydrophilic matrix and the lipophilic matrix.

10.(Amended) Compositions as claimed in claim 1, wherein the percentage of the active ingredient on the total composition weight ranges from 80 to 95%.

11.(Amended) A process for the preparation of the compositions of claim 1, which comprises:

a) melt granulation of at least one portion of the active ingredient with the lipophilic excipients with melting point lower than 90°C;

b) mixing the granules from step a) with the hydrophilic excipients and subsequent tabletting or compression.--

IN THE ABSTRACT:

Please delete the abstract as originally filed which appears on the cover sheet of the Published Application. Add new abstract as enclosed herewith on a separate sheet.

REMARKS

Claims 3, 6 and 8-11 were amended to correct multiple dependency. Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned **"VERSION WITH MARKINGS TO SHOW CHANGES MADE"**.

Respectfully submitted,

YOUNG & THOMPSON

By Benoît Castel

Benoît Castel
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December 13, 2001

"VERSION WITH MARKINGS TO SHOW CHANGES MADE"

Claims 3, 6 and 8-11 have been amended as follows:

3. (Amended) Compositions as claimed in claim 1~~ or 2~~, wherein 5-aminosalicylic acid is inglobated in the molten lipophilic matrix by kneading, extrusion and/or granulation.

6. (Amended) Compositions as claimed in ~~any one of the above claims,~~ claim 1, comprising a gastro-resistant outer coating.

8. (Amended) Compositions as claimed in ~~any one of the above claims,~~ claim 1, in the form of tablets, capsules, minitablets, wherein the active ingredient is completely contained inside the lipophilic matrix.

9. (Amended) Compositions as claimed in ~~any one of claims 1 to 7,~~ claim 1, in the form of tablets, capsules, minitablets, wherein the active ingredient is dispersed both in the hydrophilic matrix and the lipophilic matrix.

10. (Amended) Compositions as claimed in ~~any one of the above claims,~~ claim 1, wherein the percentage of the active ingredient on the total composition weight ranges from 80 to 95%.

11. (Amended) A process for the preparation of the compositions of ~~claims 1-10,~~ claim 1, which comprises:

a) melt granulation of at least one portion of the active ingredient with the lipophilic excipients with melting point lower than 90°C;

b) mixing the granules from step a) with the hydrophilic excipients and subsequent tabletting or compression.

ABSTRACT

Controlled-release oral pharmaceutical compositions containing as active ingredient 5-amino-salicylic acid, comprising: a) an inner lipophilic matrix consisting of substances with melting point below 90°C in which the active ingredient is at least partly inglobated; b) an outer hydrophilic matrix in which the lipophilic matrix is dispersed; c) optionally other excipients.

MESALAZINE CONTROLLED RELEASE ORAL PHARMACEUTICAL COMPOSITIONS

The present invention relates to controlled release oral pharmaceutical compositions containing as active ingredient 5-amino salicylic acid, also named mesalazine.

BACKGROUND OF THE INVENTION

Mesalazine is used in the treatment of Chron's disease and ulcerative colitis thanks to its antiinflammatory activity on the intestinal mucuses. Controlled-release formulations of mesalazine are disclosed in WO 95/16451, EP 0 453 001, EP 0 377 477.

The preparation of a sustained, controlled, delayed or anyhow modified release form can be carried out according to different known techniques:

1. The use of inert matrices, in which the main component of the matrix structure opposes some resistance to the penetration of the solvent due to the poor affinity towards aqueous fluids; such property being known as lipophilia.
2. The use of hydrophilic matrices, in which the main component of the matrix structure opposes high resistance to the progress of the solvent, in that the presence of strongly hydrophilic groups in its chains, mainly branched, remarkably increases viscosity inside the hydrated layer.
3. The use of bioerodible matrices, which are capable of being degraded by the enzymes of some biological compartment.

All the procedures listed above suffer, however, from drawbacks and imperfections.

Inert matrices, for example, generally entail non-linear, but esponential, release of the active ingredient.

Hydrophilic matrices have a linear behaviour until a

certain fraction of active ingredient has been released, then they significantly deviate from linear release.

Bioerodible matrices are ideal to carry out the so-called "site-release", but they involve the problem of finding the suitable enzyme or reactive to degradation. Furthermore, they frequently release in situ metabolites that are not wholly toxicologically inert.

A number of formulations based on inert lipophilic matrices have been described: Drug Dev. Ind. Pharm. 13 (6), 1001-1022, (1987) discloses a process making use of varying amounts of colloidal silica as a porization element for a lipophilic inert matrix in which the active ingredient is incorporated.

The same notion of canalization of an inert matrix is described in US 4,608,248 in which a small amount of a hydrophilic polymer is mixed with the substances forming an inert matrix, in a non sequential compenetration of different matrix materials.

EP 375,063 discloses a technique for the preparation of multiparticulate granules for the controlled-release of the active ingredient which comprises co-dissolution of polymers or suitable substances to form a inert matrix with the active ingredient and the subsequent deposition of said solution on an inert carrier which acts as the core of the device. Alternatively, the inert carrier is kneaded with the solution containing the inert polymer and the active ingredient, then the organic solvent used for the their dissolution is evaporated off to obtain a solid residue. The resulting structure is a "reservoir", i.e. is not macroscopically homogeneous along all the symmetry axis of the final form.

The same "reservoir" structure is also described in Chem. Pharm. Bull. 46 (3), 531-533,, (1998) which improves the application through an annealing technique of the inert

polymer layer which is deposited on the surface of the pellets.

To the "reservoir" structure also belong the products obtained according to the technique described in WO 93/00889 which discloses a process for the preparation of pellets in hydrophilic matrix which comprises:

- dissolution of the active ingredient with gastro-resistant hydrophilic polymers in organic solvents;
- drying of said suspension;
- subsequent kneading and formulation of the pellets in a hydrophilic or lipophilic matrix without distinction of effectiveness between the two types of application.

EP 0 453 001 discloses a multiparticulate with "reservoir" structure inserted in a hydrophilic matrix. The basic multiparticulate utilizes two coating membranes to decrease the release rate of the active ingredient, a pH-dependent membrane with the purpose of gastric protection and a pH-independent methacrylic membrane with the purpose of slowing down the penetration of the aqueous fluid.

WO 95/16451 discloses a composition only formed by a hydrophilic matrix coated with a gastro-resistant film for controlling the dissolution rate of mesalazine.

When preparing sustained-, controlled- release dosage forms of a medicament topically active in the gastrointestinal tract, it is important to ensure a controlled release from the first phases following administration, i.e. when the inert matrices have the maximum release rate inside the logarithmic phase, namely the higher deviation from linear release.

Said object has been attained by the present invention, which also allows to prepare compositions characterized by a high content in active ingredient.

DISCLOSURE OF THE INVENTION

The invention provides controlled release oral

pharmaceutical compositions containing 5-amino-salicylic acid as the active ingredient, comprising:

a) an inner lipophilic matrix consisting of substances with melting point below 90¢C in which the active ingredient is at least partially inglobated;

b) an outer hydrophilic matrix in which the lipophilic matrix is dispersed;

c) optionally other excipients.

DETAILED DISCLOSURE OF THE INVENTION

The compositions of the invention can be obtained with a method comprising the following steps:

a) the active ingredient is first inglobated in a low melting excipient or mixture of excipients, while heating to soften and/or melt the excipient itself, which thereby incorporates the active ingredient by simple dispersion.

After cooling at room temperature an inert matrix forms, which can be reduced in size to obtain matrix granules containing the active ingredient particles.

b) the inert matrix granules are subsequently mixed together with one or more hydrophilic water-swellable excipients.

This way, when the tablet is contacted with biological fluids, a high viscosity swollen layer is formed, which coordinates the solvent molecules and acts as a barrier to penetration of the aqueous fluid itself inside the new structure. Said barrier antagonizes the starting "burst effect" caused by the dissolution of the medicament inglobated inside the inert matrix, which is in its turn inside the hydrophilic matrix.

The lipophilic matrix consists of substances selected from unsaturated and/or hydrogenated fatty acids, salts, esters or amides thereof, fatty acids mono-, di- or triglycerids, waxes, ceramides, cholesterol derivatives or mixtures thereof having melting point within the range of 40

to 90°C.

If desired, a fatty acid calcium salt may be incorporated in the lipophilic matrix which is subsequently dispersed in a hydrophilic matrix prepared with alginic acid, thus remarkably increasing the hydrophilic matrix viscosity following penetration of the solvent front until contact with the lipophilic matrix granules dispersed inside.

The weight content of the active ingredient in the lipophilic matrix usually ranges from 5 to 95%.

The inert lipophilic matrix is reduced into granules by an extrusion and/or granulation process, or any other known processes which retain the homogeneous dispersion and matrix structure of the starting mixture.

The hydrophilic matrix consists of excipients known as hydrogels, i.e. substances which pass from the dry state to the hydrated one, undergo the so-called "molecular relaxation", namely a remarkable increase in mass and weight following the coordination of a large number of water molecules by the polar groups present in the polymeric chains of the excipients themselves.

Examples of hydrogels which can be used according to the invention are compounds selected from polymers or copolymers of acrylic or methacrylic acid, alkylvinyl polymers, hydroxyalkyl celluloses, carboxyalkyl celluloses, polysaccharides, dextrins, pectins, starches and derivatives, natural or synthetic gums, alginic acid.

The lipophilic matrix granules containing the active ingredient are mixed the with hydrophilic compounds cited above in a weight ratio typically ranging from 100:0.5 to 100:20 (lipophilic matrix: hydrophilic matrix). Part of mesalazine can optionally be mixed with hydrophilic substances to provide compositions in which the active ingredient is dispersed both in the lipophilic and the

hydrophilic matrix, said compositions being preferably in the form of tablets, capsules and/or minitablets.

The compression of the mixture of lipophilic matrix, hydrogel-forming compounds and, optionally, active ingredient non inglobated in the lipophilic matrix, yields a macroscopically homogeneous structure in all its volume, namely a matrix containing a dispersion of the lipophilic granules in a hydrophilic matrix.

The tablets, capsules and/or minitablets obtainable according to the invention can optionally be subjected to known coating processes with a gastro-resistant film, consisting of for example polymers of methacrylic acids (Eudragit$^{(R)}$) or cellulose derivatives, such as cellulose acetophthalate.

The compositions of the invention can contain a high percentage of active ingredient compared with the total composition weight up to 95%, an advantageous characteristic in the case of mesalazine which requires rather high unitary doses.

In terms of dissolution characteristics, the compositions of the invention provide a release profile of the active ingredient more homogeneous than the traditional systems. In fact, the immediate penetration of water inside the superficial layer of the hydrophilic matrix and the consequent swelling due to the distension of the polymeric chains of the hydrogels, gives rise to a high viscosity hydrated front which prevents the further penetration of water, linearly slowing down the dissolution process to a well determined point which can be located at about half the thickness until the further penetration of water would cause the disintegration of the hydrophilic layer and therefore the release of the content which, consisting of lipophilic granules, however induces the diffusional mechanism typical of these structures and therefore further slows down the

dissolution profile of the active ingredient.

The following examples illustrate the invention in greater detail.

Example 1

770 g of 5-aminosalicylic acid are added in a kneader with 20 g of carnauba wax and 50 g of stearic acid with heating until homogeneous dispersion, then extruded into small granules while cold.

The inert matrix granules are loaded into a mixer in which 30 g of Carbopol 971P(R) and 65 g of hydroxypropyl methylcellulose are sequentially added.

After a first mixing step for homogeneously dispersing the powders, 60 g of microcrystalline cellulose and 5 g of magnesium stearate are added. After mixing, the final mixture is tabletted to unitary weight of 649 mg/tablet or 510 mg/tablet to obtain 500 and 400 mg dosages, respectively.

The resulting tablets are film-coated with cellulose acetophthalate or polymethacrylates and a plasticizer to provide gastric resistance and prevent the early release of product in the stomach.

The dissolution profile of these tablets shows the release of an active ingredient amount lower than 30% within the first hour of permanence in simulated enteric juice, an amount lower than 60% at the fourth hour and an amount lower than 90% at the eighth hour, thus proving that the double matrix effectively controls dissolution.

Example 2

1000 g of 5-aminosalicylic acid are added in a kneader with 10 g of carnauba wax and 20 g of stearic acid with heating until homogeneous dispersion, then extruded into small granules while cold or directly granulated in a high rate mixer.

The resulting granules are loaded into a mixer in which

80 g of hydroxypropyl methylcellulose and 12 g of sodium starch glycolate are sequentially added. After a first mixing step, 11 g of silica colloidal and 11 g of magnesium stearate are added. The final mixture is homogenized, then tabletted to a unitary weight of 1144 mg/tablet.

The resulting tablets are then film coated with polymethacrylates or cellulose acetophthalate and plasticizers to provide gastric resistance.

The dissolution profile of these tablets after a lag time of permanence in the stomach and partly in the intestine provides the release of no more than 30% within the first hour, no more than 55% within two hours, no more than 70% within four hours, no more than 90% within eight hours.

Example 3

850 g of 5-aminosalicylic acid are added in granulator/kneader with 9 g of beeswax and 22 g of palmitic acid with heating, until homogeneous dispersion; then worked to a granulate in a high shear granulating device. The resulting granules are then loaded into a mixer which is added in succession with 45.5 g of hydroxypropyl methylcellulose, 45.5 g of microcrystalline cellulose, 20 g of sodium starch glycolate, 22 g of colloidal silica and 22 g of magnesium stearate. After homogenization, the final mixture is tabletted to a unitary weight of 975 mg/tablet.

The resulting tablets are then film coated with polymethacrylates or acetophthalate of cellulose and plasticizers to provide gastric resistance.

The dissolution profile of these tablets after a lag time of permanence in the stomach and partly in the intestine provides the release of no more than 30% within the first hour, no more than 50% within two hours, no more than 70% within four hours, no more than 90% within eight hours.

Example 4

1100 g of 5-aminosalicylic acid are added in granulator/kneader with 10 g of wax carnauba and 20 g of stearic acid.

10 g of polyacrylamide, 39.5 of microcrystalline cellulose and 22 g of colloidal silica are separately loaded into the homogenizer/granulator to obtain a homogeneous solid mixture, which is placed in the mixer where the active ingredient has been granulated and homogenized. 49.5 g of hydroxypropyl methylcellulose and 12 g of sodium alginate are thoroughly mixed, then added with 5 g of calcium carbonate, 34.5 g of microcrystalline cellulose and 11 g of magnesium stearate. The mixture is homogenized, then tabletted to a final unitary weight of 1194 mg/tablet. The resulting tablets are then film-coated with polymethacrylates or cellulose acetophthalate and plasticizers to provide gastric resistance.

The dissolution profile of these tablets after a lag time of permanence in the stomach and partly in the intestine provides the release of no more than 35% within the first hour, no more than 50% within two hours, no more than 70% within four hours, no more than 90% within eight hours.

Example 5

1200 g of 5-aminosalicylic acid are added in mixer with 10 g of carnauba wax and 20 g of stearic acid, with heating until homogeneous dispersion, then cold extruded into small granules or directly granulated in the high rate mixer.

The resulting granules are loaded into a mixer, then 70 g of hydroxypropyl methylcellulose and 20 g of sodium starch glycolate are sequentially added.

After a first mixing step, 80 g of sodium carbonate and 5 g of magnesium stearate are added. The final mixture is homogenized, then tabletted to unitary weight of 1375

mg/tablet.

The resulting tablets are then film-coated with polymethacrylates or cellulose acetophthalate and plasticizers to provide gastric resistance.

The dissolution profile of these tablets after a lag time of permanence in the stomach and partly in the intestine provides the release of no more than 30% within the first hour, no more than 50% within two hours, no more than 70% within four hours, no more than 90% within eight hours.

CLAIMS

1 Controlled-release oral pharmaceutical compositions containing as active ingredient 5-amino-salicylic acid, comprising:

a) an inner lipophilic matrix consisting of substances with melting point below 90°C in which the active ingredient is at least partly inglobated;

b) an outer hydrophilic matrix in which the lipophilic matrix is dispersed;

c) optionally other excipients.

2. Compositions as claimed in claim 1, wherein the lipophilic matrix consists of compounds selected from unsaturated and/or hydrogenated fatty acids, salts, esters or amides thereof, fatty acid mono-, di- or triglycerids, waxes, ceramides, cholesterol derivatives.

3. Compositions as claimed in claim 1 or 2, wherein 5-aminosalicylic acid is inglobated in the molten lipophilic matrix by kneading, extrusion and/or granulation.

4. Compositions as claimed in any one of the above claims, wherein the hydrophilic matrix consists of hydrogel-forming compounds.

5. Compositions as claimed in claim 4 wherein the hydrophilic matrix consists of compounds selected from polymers or copolymers of acrylic or methacrylic acid, alkylvinyl polymers, hydroxyalkyl celluloses, carboxyalkyl celluloses, polysaccharides, dextrins, pectins, starches and derivatives, alginic acid, natural or synthetic gums.

6. Compositions as claimed in any one of the above claims, comprising a gastro-resistant outer coating.

7. Compositions as claimed in claim 6, wherein the gastro-resistant coating consists of methacrylic acid polymers or cellulose derivatives.

8. Compositions as claimed in any one of the above claims,

in the form of tablets, capsules, minitablets, wherein the active ingredient is completely contained inside the lipophilic matrix.

9. Compositions as claimed in any one of claims 1 to 7, in the form of tablets, capsules, minitablets, wherein the active ingredient is dispersed both in the hydrophilic matrix and the lipophilic matrix.

10. Compositions as claimed in any one of the above claims, wherein the percentage of the active ingredient on the total composition weight ranges from 80 to 95%

11. A process for the preparation of the compositions of claims 1-10, which comprises:

a) melt granulation of at least one portion of the active ingredient with the lipophilic excipients with melting point lower than 90°C;

b) mixing the granules from step a) with the hydrophilic excipients and subsequent tabletting or compression.

9615V

Ref. _____

COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:
Mesalazine controlled release oral pharmaceutical compositions

the specification of which: *(check one)*

REGULAR OR DESIGN APPLICATION

[ ] is attached hereto.

[ ] was filed on _____ as application Serial No. _____ and was amended on _____ (if applicable).

PCT FILED APPLICATION ENTERING NATIONAL STAGE

[xx] was described and claimed in International application No. PCT/EP00/05321 filed on 08.06.2000 and as amended on _____ (if any).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

PRIORITY CLAIM

I hereby claim foreign priority benefits under 35 USC 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

PRIOR FOREIGN APPLICATION(S)

Country	Application Number	Date of Filing (day, month, year)	Priority Claimed
Italy	MI99A001316	14.06.1999	YES

(Complete this part only if this is a continuing application.)

I hereby claim the benefit under 35 USC 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of 35 USC 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37 Code of Federal Regulations §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.) (Filing Date) (Status--patented, pending, abandoned)

POWER OF ATTORNEY

The undersigned hereby authorizes the U.S. attorney or agent named herein to accept and follow instructions from ____ _____ as to any action to be taken in the Patent and Trademark Office regarding this application without direct communication between the U.S. attorney or agent and the undersigned. In the event of a change in the persons from whom instructions may be taken, the U.S. attorney or agent named herein will be so notified by the undersigned.

As a named inventor, I hereby appoint the following attorney(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: **Robert J. PATCH, Reg. No. 17,355, Andrew J. PATCH, Reg. No. 32,925, Robert F. HARGEST, Reg. No. 25,590, Benoît CASTEL, Reg. No. 35,041, Eric JENSEN, Reg. No. 37,855, and Thomas W. PERKINS, Reg. No. 33,027**, c/o YOUNG & THOMPSON, Second Floor, 745 South 23rd Street, Arlington, Virginia 22202.

Address all telephone calls to Young & Thompson at 703/521-2297.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor: Roberto VILLA 1-00
(given name, family name)

Inventor's signature _____ Date 30.11.2001

Residence: Edificio Vallario, Piso 6°, Calle 52 Y Ecuira Mendez, Panama City (PA) PAX Citizenship: Italian

Post Office Address: same as above

Full name of second joint inventor, if any: Massimo PEDRANI 2-00
(given name, family name)

Inventor's signature _____ Date 30.11.2001

Residence: Edificio Vallario, Piso 6°, Calle 52 Y Ecuira Mendez, Panama City (PA) PAX Citizenship: Italian

Post Office Address: same as above

Full name of third joint inventor, if any: Mauro AJANI 3-00
(given name, family name)

Inventor's signature _____ Date 30.11.2001

Residence: Edificio Vallario, Piso 6°, Calle 52 Y Ecuira Mendez, Panama City (PA) PAX Citizenship: Italian

Post Office Address: same as above

Full name of fourth joint inventor, if any Lorenzo FOSSATI 4-a

Inventor's signature _____ 30.11.2001 Date

Residence Edificio Vallario, Piso 6°, Calle 52 Y Ecuira Mendez, ~~Panama City (PA)~~ PAX

Citizenship Italian

Post Office Address same as above

Full name of fifth joint inventor, if any _____

Inventor's signature _____ Date

Residence _____

Citizenship _____

Post Office Address _____

Full name of sixth joint inventor, if any _____

Inventor's signature _____ Date

Residence _____

Citizenship _____

Post Office Address _____

Full name of seventh joint inventor, if any _____

Inventor's signature _____ Date

Residence _____

Citizenship _____

Post Office Address _____

Full name of eighth joint inventor, if any _____

Inventor's signature _____ Date

Residence _____

Citizenship _____

Post Office Address _____